

contd.
B¹

this CCR5 antagonistic activity and is suitable for oral administration. The present invention is to provide a novel anilide derivative which is useful for the treatment or prevention of infectious diseases of HIV and, in particular, AIDS and also which is suitable for oral administration, production and use thereof.

Please insert the following paragraph as the first paragraph on page 6 of the specification.

Page 6, paragraph 1 (AMENDED)

B²

- (18) The compound as described in the above (17), wherein the alicyclic hydrocarbon group is a lower cycloalkyl group;
- (19) The compound as described in the above (17), wherein the alicyclic hydrocarbon group is cyclohexyl;
- (20) The compound as described in the above (17), wherein the alicyclic heterocyclic group is a saturated alicyclic heterocyclic group;
- (21) The compound as described in the above (17), wherein the alicyclic heterocyclic group is tetrahydropyranyl, tetrahydrothiopyranyl or piperidyl;
- (22) The compound as described in the above (17), wherein the alicyclic heterocyclic group is tetrahydropyranyl;
- (23) The compound selected from the class consisting of 7-(4-ethoxyethoxyphenyl)-1-ethyl-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide; 1-ethyl-7-(4-propoxyethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide; 7-(4-butoxyethoxyphenyl)-1-ethyl-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide; 7-(4-ethoxyethoxyphenyl)-1-formyl-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-

Please insert the following paragraph as the first paragraph on page 12 of the specification.

✓ Page 12, paragraph 1 (AMENDED) ✓

B³

treatment or prevention of infectious diseases of HIV;

(36) A method for antagonizing a CC chemokine receptor (CCR) in a mammal, which comprises administering an effective amount of a compound described in the above (1) or a salt thereof to a mammal;

(37) Use of a compound described in the above (1) or a salt thereof in preparation of a medicament for antagonizing a CC chemokine receptor (CCR); etc.

10018321-121201

Please insert the following paragraph as the first paragraph on page 14 of the specification.

✓ Page 14, paragraph 1 (AMENDED) ✓

B⁴

as cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl, etc.), and the like.

Please insert the following paragraph as the first paragraph on page 16 of the specification.

✓ Page 16, paragraph 1 (AMENDED) ✓

B⁵

pyrazolidine, pyrazoline, piperidine, piperazine, oxazine, oxadiazine, thiazine, thiadiazine, morpholine, thiomorpholine, pyran and tetrahydropyran, as well as non-aromatic heterocycles in which some or all of the bonds of the aforementioned non-aromatic heterocycle are saturated bonds, and the like (preferably, aromatic heterocycles such as pyrazole, thiazole, oxazole, tetrazole, etc.).

Please insert the following paragraph as the first paragraph on page 19 of the specification.

✓ Page 19, paragraph 1 (AMENDED) ✓

B6

of the C₃₋₇ cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc. Among others, a straight C₁₋₆ lower alkyl is preferable and C₁₋₃ lower alkyl is more preferable. The groups R⁷ and R⁸ may be the same or different, and preferably the groups R⁷ and R⁸ are the same. When R⁷ and R⁸ may bind to each other to form a 5- to 7- membered ring, the groups R⁷ and R⁸ bind to each other to represent a straight C₂₋₄ alkylene chain of the formula: -(CH₂)₂-, -(CH₂)₃-, -(CH₂)₄-, etc. Said chain may have a substituent, and examples of the substituent include hydroxy group, halogen, etc.

Please insert the following paragraph as the second paragraph on page 19 of the specification.

✓ Page 19, paragraph 2 (AMENDED) ✓

B7

Examples of the optionally esterified carboxyl group include a carboxyl group and an ester formed by binding a carboxyl group to a C₁₋₆ alkyl group or a C₃₋₇ cycloalkyl group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxy-carbonyl, pentyloxycarbonyl, hexyloxycarbonyl, etc.).

Please insert the following paragraph as the first paragraph on page 22 of the specification.

Page 22, paragraph 1 (AMENDED)

B8

methoxymethoxy, methoxyethoxy, ethoxyethoxy, trifluoromethoxyethoxy, trifluoroethoxyethoxy, etc.), formyl, C₂₋₄ alkanoyl (e.g. acetyl, propionyl, etc.), C₁₋₄ alkylsulfonyl

contd.
B8

(e.g. methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of substituents is preferably 1 to 3.

Please insert the following paragraph as the first paragraph on page 31 of the specification.

Page 31, paragraph 1 (AMENDED)

B9

sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, octyl, nonyl, decyl, etc., preferably lower (C_{1-6}) alkyl, etc.);

(3) an optionally substituted cycloalkyl (e.g. C_{3-7} cycloalkyl, etc. such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.);

(4) an optionally substituted alkenyl (e.g., C_{2-10} alkenyl such as allyl, crotyl, 2-pentenyl, 3-hexenyl, etc., preferably lower (C_{2-6}) alkenyl, etc.);

(5) an optionally substituted cycloalkenyl (e.g. C_{3-7} cycloalkenyl, etc. such as 2-cyclopentenyl, 2-cyclohexenyl, 2-cyclopentenylmethyl, 2-cyclohexenylmethyl, etc.);

(6) an optionally substituted 5-to 6-membered monocyclic aromatic group (e.g., phenyl, 5-to 6-membered aromatic heterocyclic group (e.g., 5- to 6-membered aromatic heterocyclic group containing 1 to 4 hetero-atoms consisting of 1 to 2 kinds of hetero-atoms selected from oxygen atom, sulfur atom and nitrogen atom, such as furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, isothiazolyl, isoxazolyl, tetrazolyl, pyridyl, pyrazyl, pyrimidinyl, pyridazinyl, triazolyl, etc.);

(7) an optionally substituted 5- to 6-membered monocyclic non-aromatic heterocyclic group (e.g., a group which is formed by removing one hydrogen atom from a 5- to 6-

10018321-121201

Please insert the following paragraph as the first paragraph on page 33 of the specification.

Page 33, paragraph 1 (AMENDED) ✓

B10

substituted thiol group (e.g., thiol, C₁₋₄ alkylthio, etc.), an optionally substituted amino group (e.g., amino; mono-C₁₋₄ alkylamino; di-C₁₋₄ alkylamino; 5- to 6- membered cyclic amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole, etc.; etc.), an optionally esterified or amidated carboxyl group (e.g. carboxyl, C₁₋₄ alkoxy-carbonyl, carbamoyl, mono-C₁₋₄ alkylcarbamoyl, di-C₁₋₄ alkylcarbamoyl, etc.), an optionally halogenated C₁₋₄ alkyl (e.g., trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C₁₋₄ alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy, etc.), C₁₋₄ alkylenedioxy (e.g., -O-CH₂-O-, -O-CH₂-CH₂-O-, etc.), optionally substituted sulfonamide [e.g., an optionally substituted amino group (e.g. amino; mono-C₁₋₄ alkylamino; di-C₁₋₄ alkylamino; 5- to 6- membered cyclic amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole, etc.) which is bound to -SO₂-, etc.], formyl, C₂₋₄ alkanoyl (e.g., acetyl, propionyl, etc.), C₁₋₄ alkylsulfonyl (e.g., methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of the substituents are preferably 1 to 3.

10018321.121201

Please insert the following paragraph as the first paragraph on page 35 of the specification.

Page 35, paragraph 1 (AMENDED) ✓

B11

include halogen (e.g., fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, an optionally substituted thiol group (e.g., thiol, C₁₋₄ alkylthio, etc.), an optionally substituted amino group (e.g., amino; mono-C₁₋₄ alkylamino; di-C₁₋₄ alkylamino; 5- to 6- membered cyclic amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole, etc.; etc.), an optionally esterified or amidated carboxyl group (e.g., carboxyl, C₁₋₄

contd.
B11

alkoxycarbonyl, carbamoyl, mono-C₁₋₄ alkyl carbamoyl, di-C₁₋₄ alkylcarbamoyl, etc.), an optionally halogenated C₁₋₄ alkyl, (e.g., trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C₁₋₄ alkoxy (e.g., methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy, etc.), formyl, C₂₋₄ alkanoyl (e.g., acetyl, propionyl, etc.) C₁₋₄ alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of substituents is preferably 1 to 3.

Please insert the following paragraph as the second paragraph on page 35 of the specification.

✓ Page 35, paragraph 2 (AMENDED) ✓

B12
10018321-121201

Examples of the optionally amidated carboxyl group as the substituent for R¹ include a carbonyl group binding to "an optionally substituted amino group", etc. which is the same as that of the above-described "optionally substituted amino group as the substituents for R¹" and among others, carbamoyl, mono-C₁₋₆ alkylcarbamoyl, di-C₁₋₆ alkylcarbamoyl, etc. are

Please insert the following paragraph as the first paragraph on page 38 of the specification.

✓ Page 38, paragraph 1 (AMENDED) ✓

B13

aromatic ring which has a group of the formula: R-Z¹-X-Z²- wherein each symbol is as defined above, and which may have a further substituent" represented by R¹ may have, in addition to the group of the formula: R-Z¹-X-Z²-, include, in particular, a lower (C₁₋₄) alkyl optionally substituted with a halogen or a lower (C₁₋₄) alkoxy (e.g., methyl, ethyl, t-butyl, trifluoromethyl, methoxymethyl, ethoxymethyl, propoxymethyl, butoxymethyl, methoxyethyl, ethoxyethoxy, propoxyethyl, butoxyethyl, etc.), a lower (C₁₋₄) alkoxy optionally substituted with a halogen or a lower (C₁₋₄) alkoxy (e.g., methoxy, ethoxy, propoxy, butoxy, t-butoxy, trifluoromethoxy, methoxymethoxy, ethoxymethoxy, propoxymethoxy, butoxymethoxy, methoxyethoxy,

ethoxyethoxy, propoxyethoxy, butoxyethoxy, methoxypropoxy, ethoxypropoxy, propoxypropoxy, butoxypropoxy, etc.), halogen (e.g., fluorine, chlorine, etc.), nitro, cyano, an amino group optionally substituted with 1-2 lower (C₁₋₄) alkyl groups, formyl group or lower (C₂₋₄) alkanoyl groups (e.g., amino, methylamino, dimethylamino, formylamino, acetylamino, etc.), 5- to 6-membered cyclic amino (e.g., 1-pyrrolidinyl, 1-piperazinyl, 1-piperidinyl, 4-morpholino, 4-thiomorpholino, 1-imidazolyl, 4-tetrahydropyranyl, etc.), etc.

Please insert the following paragraph as the second paragraph on page 41 of the specification.

五、三、二、一

In the above formula (I), examples of the “optionally substituted aliphatic hydrocarbon group” (aliphatic straight chain hydrocarbon group and aliphatic cyclic hydrocarbon group) represented by R^2 and R^3 include (1) an optionally substituted alkyl (e.g., C_{1-10} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc., preferably lower (C_{1-6}) alkyl, etc.); (2) an optionally substituted cycloalkyl (e.g. C_{3-8} cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, etc.; etc.), provided that (2-1) said cycloalkyl may contain one hetero-atom selected from a sulfur atom, an oxygen atom and a nitrogen atom to form oxirane, thiolane, aziridine, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, tetrahydropyran, tetrahydrothiopyran, tetrahydrothiopyran-1-oxide, piperidine, etc. (preferably, 6-membered ring

Please insert the following paragraph as the second paragraph on page 47 of the specification.

✓ Page 47, paragraph 2 (AMENDED) ✓

B15

As the compound represented by the above formula (I), 7-(4-ethoxyethoxyphenyl)-1-ethyl-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide; 1-ethyl-7-(4-propoxyethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide; 7-(4-butoxyethoxyphenyl)-1-ethyl-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide; 7-(4-ethoxyethoxyphenyl)-1-formyl-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide; 1-formyl-7-(4-propoxyethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide; 7-(4-butoxyethoxyphenyl)-1-formyl-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide; 7-(4-butoxyethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-5-yl)amino]methyl]phenyl]-1-propyl-2,3-dihydro-1-benzazepine-4-carboxamide; N-[4-[[N-methyl-N-(tetrahydropyran-5-

100103221-121201

Please insert the following paragraph as the first paragraph on page 54 of the specification.

✓ Page 54, paragraph 1 (AMENDED) ✓

B16

antioxidant, a colorant, a sweetener, etc. may be used. Suitable examples of the excipient include lactose, sucrose, D-mannitol, starch, crystalline cellulose, light silicic acid anhydride, etc. Suitable examples of the lubricant include magnesium stearate, calcium stearate, talc, colloidal silica, etc. Suitable examples of the binder include crystalline cellulose, sucrose, D-mannitol, dextrin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinyl-pyrrolidone, etc.

contd.

B16

Suitable examples of the disintegrating agent include starch, carboxymethyl cellulose, carboxymethyl cellulose calcium, croscarmellose sodium, sodium carboxymethyl starch, etc. Suitable examples of the solvent include water for injection, alcohol, propylene glycol, macrogol, sesame oil, corn oil, etc. Suitable examples of the solubilizer include polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate, etc. Suitable examples of the suspending agent include surfactants such as stearyl triethanolamine, sodium laurylsulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride, glycerin monostearate, etc.; hydrophilic polymers such as polyvinylalcohol, polyvinylpyrrolidone, sodium carboxymethyl cellulose, methyl cellulose, hydroxymethyl

Please insert the following paragraph as the first paragraph on page 55 of the specification.

✓ Page 55, paragraph 1 (AMENDED) ✓

B17

cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, etc. Suitable examples of the isotonicizing agent include sodium chloride, glycerin, D-mannitol, etc. Suitable examples of the buffer include a buffer solution of phosphate, acetate, carbonate, citrate, etc. Suitable examples of the soothing agent include benzylalcohol, etc. Suitable examples of the preservative include p-hydroxybenzoic acid esters, chlorobutanol, benzylalcohol, phenethylalcohol, dehydroacetic acid, sorbic acid, etc. Suitable examples of the antioxidant include sulfites, ascorbic acid, etc.

Please insert the following paragraph as the first paragraph on page 61 of the specification.

✓ Page 61, paragraph 1 (AMENDED) ✓

B18

(1) Compound (I) can be produced by reacting Compound (I-1) or (I-2) with halogenated alkyl or halogenated aralkyl. Examples of a halogen atom include chlorine, bromine, iodine, etc. and usually about 1 to 2 moles of the halogenated alkyl or halogenated aralkyl is used per mole of Compound (I-1) or (I-2). If necessary, the reaction smoothly proceeds by addition of about equal to three-fold moles of a base such as triethylamine, diisopropylethylamine, pyridine, lithium hydride, sodium

Please insert the following paragraph as the second paragraph on page 64 of the specification.

✓ Page 64, paragraph 2 (AMENDED) ✓

B19

Compound (I) having a tertiary amino group can be produced by reacting Compound (IV) and a secondary amine compound. Usually, about 1 to 3 moles of the secondary amine compound is used per mole of Compound (IV). If necessary, the reaction smoothly proceeds by addition of about equal to three-fold moles of a base such as triethylamine, diisopropylethylamine, pyridine, lithium hydride, sodium hydride, sodium methoxide, sodium ethoxide, sodium carbonate, potassium carbonate, sodium hydrogen carbonate and further sodium iodide, potassium iodide, etc. This substitution reaction is carried out in an inert solvent such as methanol, ethanol, propanol, isopropanol, n-butanol, tetrahydrofuran, diethyl ether, dimethoxyethane, 1,4-dioxane, toluene, benzene, xylene, dichloromethane, chloroform, 1,2-dichloroethane, dimethylformamide (DMF), dimethyl sulfoxide (DMSO), pyridine, etc., or a mixture of these solvents. The reaction temperature is generally about -10°C to about 180°C ,

contd
B19

and the reaction time is generally about 1 hour to about 40 hours. The reaction is carried out preferably under inert gas (e.g. nitrogen, argon, etc.) atmosphere.

[Method D]

Please insert the following paragraph as the second paragraph on page 71 of the specification.

✓ Page 71, paragraph 2 (AMENDED) ✓

B20

The resultant Compound (II) or (III) can be separated and purified with known separation and purification methods such as concentration, concentration under reduced pressure, extraction, crystallization, solvent conversion, chromatography, etc.

10018321.122B1001

Please insert the following paragraph as the second paragraph on page 75 of the specification.

✓ Page 75, paragraph 2 (AMENDED) ✓

B21

When the compound of the formula (I) or a salt thereof is used in combination with a reverse transcriptase inhibitor and/or a protease inhibitor, the dose of the reverse transcriptase inhibitor or the protease inhibitor ranges, for example, from about 1/200-1/2 or more of the usual dose to about 2-3 times or less of the usual dose. In case that two or more drugs are used in combination, each dose of the drugs is appropriately adjusted if one drug affects metabolism of the other drug, while each dose of the drugs when they are used in combination is generally the same as the dose when they are used alone.

Please insert the following paragraph as the first paragraph on page 79 of the specification.

✓ Page 79, paragraph 1 (AMENDED) ✓

B22

flask (Becton Dickinson) using Ham's F12 medium (Nihon Pharmaceutical) containing 10% fetal calf serum (Life Tech Oriental) and taken off with 0.5 g/L trypsin-0.2g/L EDTA (Life Tech Oriental). The cells were washed with PBS (Life Tech Oriental), centrifuged (1000 rpm, 5 minutes), and suspended in PBS. With using Gene Pulser (Bio-Rad Laboratories), DNA was introduced into the cells under the conditions shown below. That is, to the cuvette of 0.4 cm gap were added 8×10^6 cells and 10 μ g of plasmid pCKR5 for expression of human CCR5, and electroporation was carried out under 0.25 kV of voltage and 960 μ F of capacitance. The cells were transferred into Ham's F12 medium containing 10% fetal calf serum, and cultivated for 24 hours. The cells were again taken off and centrifuged, and suspended in Ham's F12 medium containing 10% fetal calf serum and 500 μ g/ml of geneticin (Life Tech Oriental). The suspension was diluted to give 104 cells/ml of the suspension, which was inoculated on a 96 well plate (Becton Dickinson) to give geneticin resistant cells.

10018321.124201
T02F2T T2E8T00T

Please insert the following paragraph as the first paragraph on page 83 of the specification.

✓ Page 83, paragraph 1 (AMENDED) ✓

B23

potassium ferricyanide, 2 μ M $MgCl_2$ and 0.4 mg/ml X-gal), and the mixture was allowed to stand at 37 °C for 50 minutes and washed twice with PBS. The number of blue cells was counted by a microscope and defined as the number of cells infected with HIV-1. According to this method, inhibition rate of HIV-1 infection was determined. The results are shown in Table 2.

Please insert the following paragraph as the first paragraph on page 90 of the specification.

✓ Page 90, paragraph 1 (AMENDED) ✓

B24

In DMF (12 ml) was suspended 7-(4-ethoxyphenyl)-1-methanesulfonyl-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.13 g). To the suspension was added, under ice-cooling, thionyl chloride (0.04 ml) and DMF (catalytic amount), and the mixture was stirred at room temperature for 2 hours. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in THF (15 ml). The solution was added dropwise to a solution of 4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]aniline (0.08 g) and triethylamine (0.14 ml) in THF (5 ml), under ice-cooling, and the mixture was stirred under nitrogen atmosphere at room temperature overnight. Under reduced pressure, the solvent was evaporated. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate/hexane to give 7-(4-ethoxyphenyl)-1-methanesulfonyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (0.16 g) as colorless crystals.

Please insert the following paragraph as the second paragraph on page 98 of the specification.

✓ Page 98, paragraph 2 (AMENDED) ✓

Reference Example 11

B25

In water: ethanol: toluene (1:1: 10, v/v, 18.0 ml) were dissolved 4-propoxyphenyl borate (203 mg) and 7-bromo-1-methyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-benzazepine-4-carboxamide (455 mg). To the

contd.
B 25

solution was added potassium carbonate (312 mg), and the mixture was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium

Please insert the following paragraph as the first paragraph on page 103 of the specification.

✓ Page 103, paragraph 1 (AMENDED) ✓

B 26

10018321.121201

the mixture was stirred at room temperature for 1 hour. Under reduced pressure, the solvent was evaporated, and to the residue was added THF (10.0 ml). On the other hand, to 4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]aniline dihydrochloride (158 mg) was added THF (10.0 ml), and then was added triethylamine (0.47 ml). To the obtained mixture was added dropwise at 0 °C the previously prepared acid chloride suspension, and the mixture was stirred at room temperature for 3 hours. To the mixture was added ethyl acetate, and the mixture was washed with water, 1N sodium hydroxide solution, water and saturated brine. The organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (15 g, ethyl acetate → ethyl acetate: ethanol: triethylamine = 100: 10: 1), and recrystallized from ethanol to give 7-(4-ethoxy-3-fluorophenyl)-1-methylsulfonyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (140 mg, 51 %) as white crystals.

Please insert the following paragraph as the first paragraph on page 106 of the specification.

✓ Page 106, paragraph 1 (AMENDED) ✓

B27 bromobutyrate (82 ml). The mixture was stirred under nitrogen atmosphere at 85 °C for 24 hours, and to the mixture was added potassium t-butoxide (70 g) under ice-cooling. The mixture was stirred at 85 °C for 1.5 hours, and the solvent was evaporated. To the residue was added ice-water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated to give ethyl (methyl) 7-bromo-5-hydroxy-1-tosyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (mixture) (153 g) as white crystals.

Please insert the following paragraph as the second paragraph on page 111 of the specification.

✓ Page 111, paragraph 2 (AMENDED) ✓

Reference Example 22

B28 To anhydrous acetic acid (0.84 ml) was added dropwise formic acid (0.4 ml), under ice-cooling, and the mixture was stirred, under nitrogen atmosphere, at 50 °C for 2 hours. To the mixture was added THF (5 ml), and to the mixture was added dropwise, under ice-cooling, a solution of methyl 7-bromo-2,3-dihydro-1H-1-benzazepine-4-carboxylate (1.0 g) in THF (15 ml). The mixture was stirred at room temperature overnight. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with sodium hydrogen carbonate solution, water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated to give methyl 7-bromo-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (1.07 g) as colorless crystals.

Please insert the following paragraph as the second paragraph on page 133 of the specification.

✓ Page 133, paragraph 2 (AMENDED) ✓

B 29

Reference Example 46

In methanol (25 ml) and THF (25 ml) was dissolved methyl 7-[4-(2-butoxyethoxy)phenyl]-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.23 g). To the solution was added 1N sodium hydroxide solution (5 ml), and the mixture was stirred at 55 °C for 1.5 hours and concentrated. To the residue was added water, and the mixture was neutralized with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated to give 7-[4-(2-butoxyethoxy)phenyl]-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.24 g) as colorless amorphous.

10018321.121201

Please insert the following paragraph as the second paragraph on page 154 of the specification.

✓ Page 154, paragraph 2 (AMENDED) ✓

B 30

Reference Example 68

In a mixture of THF and ethanol (1:1, v/v, 10.0 ml) was dissolved methyl 1-acetyl-7-[4-(4-morpholino)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (394 mg). To the solution was added 1N sodium hydroxide solution (3.0 ml), and the mixture was stirred at room temperature for 12 hours. To the mixture was added 1N hydrochloric acid to convert to a weakly acidic solution, and the mixture was extracted with ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give 1-acetyl-7-[4-(4-morpholino)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (372 mg, 98%) as pale yellow crystals.

Please insert the following paragraph as the first paragraph on page 157 of the specification.

✓ Page 157, paragraph 1 (AMENDED) ✓

10048324 421304
T03T2T T2E8T001

31 mixture was heated to reflux under argon atmosphere for 14.5 hours. The mixture was diluted with ethyl acetate, and washed with water and saturated brine, and the organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (75 g, hexane: ethyl acetate = 3 : 1) to give methyl 1-(t-butoxycarbonyl)-7-(4-propoxyphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate as yellow amorphous. The obtained methyl 1-(t-butoxycarbonyl)-7-(4-propoxyphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate was dissolved in ethyl acetate (80 ml). To the solution was added 6N hydrochloric acid (20 ml) at room temperature, and the mixture was stirred at 100°C for 30 minutes and neutralized with 1N sodium hydroxide and saturated sodium hydrogen carbonate solution. The separated organic layer was washed with saturated sodium hydrogen carbonate solution, water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give crystals, which were washed with ethyl acetate/hexane to give methyl 7-(4-propoxyphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (947 mg) as yellow crystals. The mother liquor was concentrated, and the residue was purified with silica gel column chromatography (15 g, hexane:ethyl

Please insert the following paragraph as the first paragraph on page 163 of the specification.

✓ Page 163, paragraph 1 (AMENDED) ✓

32 the residue was purified with silica gel column chromatography (75 g, hexane: ethyl acetate = 4:1) to give methyl 1-(t-butoxycarbonyl)-7-(4-ethoxy-3-fluorophenyl)-2,3-dihydro-1H-1-

contd.
B32

benzazepine-4-carboxylate as yellow amorphous. The obtained methyl 1-(t-butoxycarbonyl)-7-(4-ethoxy-3-fluorophenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate was dissolved in ethyl acetate (80 ml). To the solution was added 1N hydrochloric acid (15 ml) at room temperature, and the mixture was stirred at 100 °C for 1 hour and neutralized with 1N sodium hydroxide and saturated sodium hydrogen carbonate solution. To the mixture was added ethyl acetate, and the separated organic layer was washed with saturated sodium hydrogen carbonate solution, water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (50 g, hexane: ethyl acetate = 9: 1 → 4:1 → 2: 1) to give methyl 7-(4-ethoxy-3-fluorophenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (1007 mg, 86 %) as yellow crystals.

Please insert the following paragraph as the first paragraph on page 188 of the specification.

✓ Page 188, paragraph 1 (AMENDED) ✓

Working Example 1 (Production of Compound 1)

In DMF (10 ml) was dissolved 7-[4-(2-ethoxyethoxy)phenyl]-1-formyl-2,3-dihydro-1H-1-benzazepine 4-carboxylic acid (0.18 g). To the solution was added, under ice-cooling, thionyl chloride (0.09 ml), and the mixture was stirred at room temperature for 30 minutes. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in THF (20 ml). The solution was added dropwise to a solution of 4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]aniline (0.12 g) and triethylamine (0.33 ml) in THF (10 ml), under ice-cooling, and the mixture was stirred under nitrogen atmosphere at room temperature overnight. Under reduced pressure, the solvent was evaporated. To the residue was added water, and the mixture

contd.
B33

was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate/hexane to give 7-[4-(2-ethoxyethoxy)phenyl]-1-formyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 1) (0.23g) as colorless crystals.

Please insert the following paragraph as the first paragraph on page 191 of the specification.

Page 191, paragraph 1 (AMENDED) ✓

B34

10018721
12281001
102121

and the mixture was stirred at room temperature for 30 minutes. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in THF (25 ml). The solution was added dropwise to a solution of 4-[N-methyl-N-(tetrahydro-3H-pyran-4-yl)aminomethyl]aniline (0.15 g), and triethylamine (0.4 ml) in THF (5 ml), under ice-cooling, and the mixture was stirred under nitrogen atmosphere at room temperature overnight. Under reduced pressure, the solvent was evaporated. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated to give crude crystals, which were recrystallized from ethanol to give 7-[4-(2-butoxyethoxy)phenyl]-1-formyl-N-[[4-[(N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino)methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 3) (0.23 g) as colorless crystals.

Please insert the following paragraph as the second paragraph on page 197 of the specification.

✓ Page 197, paragraph 2 (AMENDED) ✓

B35

Working Example 8 (Production of Compound 8)

In THF (5 ml) was dissolved 7-[4-(3-ethoxypropoxy)phenyl]-1-methanesulfonyl-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.20 g). To the solution were added, under ice-cooling, thionyl chloride (0.06 ml) and DMF (catalytic amount), and the mixture was stirred at room temperature for 2 hours. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in THF (15 ml). The solution was added dropwise to a solution of 4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]aniline (0.11 g) and triethylamine (0.19 ml) in THF (5 ml), under ice-cooling, and the mixture was

Please insert the following paragraph as the second paragraph on page 203 of the specification.

✓ Page 203, paragraph 2 (AMENDED) ✓

B36

Working Example 12 (Production of Compound 12)

In a mixture of water: ethanol: toluene (1: 1: 10, v/v, 18.0 ml) were dissolved 4-(2-propoxyethoxy)phenyl borate (242 mg) and 7-bromo-1-methyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (436 mg). To the solution was added potassium carbonate (299 mg), and the mixture was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (42 mg), and the mixture was heated to reflux under argon atmosphere for 10 hours. The mixture was diluted with ethyl acetate, and washed with water and saturated brine, and the organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column

contd
B36

chromatography (30 g, ethyl acetate: ethanol: triethylamine = 180: 20: 1) and recrystallized from ethanol/hexane to give 1-methyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1H-benzazepine-4-carboxamide (Compound 12) (186 mg, 35%) as yellow crystals.

Please insert the following paragraph as the first paragraph on page 206 of the specification.

✓ Page 206, paragraph 1 (AMENDED) ✓

B37

10018321.121201

room temperature for 30 minutes. Under reduced pressure, the solvent was evaporated, and to the residue was added THF (15.0 ml). On the other hand, to 4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]aniline dihydrochloride (337 mg) was added THF (10.0 ml), and then was added triethylamine (1.00 ml). To the obtained mixture was added dropwise at 0 °C the previously prepared acid chloride suspension, and the mixture was stirred at room temperature for 15 hours. To the mixture was added ethyl acetate, and the mixture was washed with water and saturated brine. The organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (35 g, ethyl acetate → ethyl acetate: ethanol = 10: 1 → ethyl acetate: ethanol: triethylamine = 100: 10: 1) and recrystallized from ethanol to give 1-formyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-7-[4-(2-propoxy)ethoxyphenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 14) (459 mg, 80 %) as white crystals.

Please insert the following paragraph as the first paragraph on page 212 of the specification.

✓ Page 212, paragraph 1 (AMENDED) ✓

B38

10018321-121201
dihydro-1H-1-benzazepine-4-carboxamide (440 mg). To the solution was added potassium carbonate (301 mg), and the mixture was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (42 mg), and the mixture was refluxed under argon atmosphere for 10 hours. The mixture was diluted with ethyl acetate, and washed with water and saturated brine, and the organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (30 g, ethyl acetate → ethyl acetate: ethanol = 10: 1 → ethyl acetate: ethanol: triethylamine = 100: 10: 0.5) and recrystallized from ethyl acetate/IPE to give 7-[4-(2-butoxyethoxy)phenyl]-1-methyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 18) (287 mg, 53 %) as yellow crystals.

Please insert the following paragraph as the second paragraph on page 216 of the specification.

Page 216, paragraph 2 (AMENDED)

Working Example 21 (Production of Compound 21)

B39

In a mixture of water: ethanol: toluene (1: 1: 10; v/v, 18.0 ml) were dissolved 3-chloro-4-(2-ethoxy)ethoxyphenyl borate (280 mg) and 7-bromo-1-formyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (380 mg). To the solution was added potassium carbonate (253 mg), and the mixture was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (35 mg), and the mixture was heated to reflux under argon

contd.

B39

atmosphere for 10 hours. The mixture was diluted with ethyl acetate, and washed with water and saturated brine, and the organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (25 g, ethyl acetate → ethyl acetate: ethanol = 10: 1 → ethyl acetate: ethanol: triethylamine = 100 : 10: 0.5) and recrystallized from ethanol to give 7-[3-chloro-4-(2-ethoxy)ethoxyphenyl]-1-

Please insert the following paragraph as the second paragraph on page 228 of the specification.

✓ Page 228, paragraph 2 (AMENDED) ✓

B40

Working Example 30 (Production of Compound 30)

In DMF (6 ml) was dissolved 1-butyl-7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.30 g). Under ice-cooling, to the mixture was added thionyl chloride (0.15 ml). The mixture was stirred at room temperature for 30 minutes. The solvent was evaporated under reduced pressure. In THF (20 ml) was suspended the residue, and the suspension was added dropwise to a solution of 4-[N-methyl-N-

Please insert the following paragraph as the second paragraph on page 231 of the specification.

✓ Page 231, paragraph 2 (AMENDED) ✓

B41

Working Example 32 (Production of Compound 32)

In DMF (4 ml) was dissolved 1-benzyl-7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.15 g). Under ice-cooling, to the mixture was added thionyl chloride (0.06 ml). The mixture was stirred at room temperature for 30 minutes. The solvent was evaporated under reduced pressure. In THF (25 ml) was dissolved the residue, and then the

contd.

B41

solution was added dropwise to a solution of 4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]aniline (0.09 g) and triethylamine (0.23 ml) in THF (10 ml), under ice-cooling. The mixture was stirred at room temperature overnight under nitrogen atmosphere. The solvent was evaporated under reduced pressure. Water was added to the mixture, and then the mixture was extracted with ethyl acetate. The organic layer was

Please insert the following paragraph as the second paragraph on page 255 of the specification.

✓ Page 255, paragraph 2 (AMENDED) ✓

B42

Reference Example 99

In methanol (25 ml) and THF (25 ml) was dissolved methyl 1-propionyl-7-(2-propoxyethoxy)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.2 g), and to the solution was added 1N sodium hydroxide solution (5 ml). The mixture was stirred at room temperature overnight, concentrated, and then neutralized with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated to give 1-propionyl-7-(2-propoxyethoxy)-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.2 g) as colorless crystals.

Please insert the following paragraph as the second paragraph on page 263 of the specification.

✓ Page 263, paragraph 2 (AMENDED) ✓

B43

Reference Example 109

In methanol (10 ml) and THF (10 ml) was dissolved methyl 1-benzyl-7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.27 g). To the solution was added 1N sodium hydroxide solution (10 ml), and the mixture was stirred at room

contd.
B43

temperature overnight

Please insert the following paragraph as the second paragraph on page 265 of the specification.

✓ Page 265, paragraph 2 (AMENDED) ✓

B44

Reference Example 111

In methanol (25 ml) and THF (25 ml) was dissolved methyl 1-benzyl-7-[4-(2-butoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.49 g). To the solution was added 1N sodium hydroxide solution (10 ml), and the mixture was heated at 50 °C overnight and concentrated, then neutralized with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated to give 1-benzyl-7-[4-(2-butoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.47 g) as yellow crystals.

1001833P1 1E1E01

Please insert the following paragraph as the second paragraph on page 343 of the specification.

✓ Page 343, paragraph 2 (AMENDED) ✓

B45

Working Example 81 (Production of Compound 81)

A catalytic amount of N,N-dimethyl-4-aminopyridine was added to a solution of 7-butoxyethoxyphenyl)-1-[(4-methylthiazol-5-yl)methyl]-2,3-dihydro-1-benzazepine-4-carboxylic acid (150 mg), 4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]aniline (88 mg) and 1-hydroxybenzotriazole (96 mg) in DMF (15 ml), followed by addition of 1-ethyl-3-(3-dimethylaminopropylcarbodiimide (137 mg). The mixture was stirred under nitrogen atmosphere at room temperature overnight. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried

contd.
B45

with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was separated and purified with silica gel column chromatography (methanol: ethyl acetate = 1:3) to give 7-(4-butoxyethoxyphenyl)-N-[4-[[N-methyl-N-tetrahydropyran-5-yl)amino]methyl]phenyl]-1-[(4-methylthiazol-5-yl)methyl]-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 81) (7 mg) as yellow amorphous.

Please insert the following paragraph as the second paragraph on page 351 of the specification.

✓ Page 351, paragraph 2 (AMENDED) ✓

B46
10013321 1231001
102121 1231001

Reference Example 153

To a solution of methyl 7-(propoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylate (300 mg) and 2-methoxybenzaldehyde (535 mg) in 1,2-dichloroethane (10 ml) was added sodium triacetoxyborohydride (749 mg), and the mixture was stirred under nitrogen atmosphere at room temperature overnight. Then, water was added thereto and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure and the resulting residue was purified with silica gel column chromatography (hexane: ethyl acetate = 3:1) to give methyl (1-(2-methoxybenzyl)-7-(4-propoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylate (394 mg) as yellow oil.

Please insert the following paragraph as the second paragraph on page 355 of the specification.

✓ Page 355, paragraph 2 (AMENDED) ✓

B47

Reference Example 157

To a suspension of 60% sodium hydride (0.23 g) in tetrahydrofuran (5 ml) which had

contd.
B47

been washed with hexane three times was added dropwise a solution of methyl 7-bromo-2,3-dihydro-1-benzazepine-4-carboxylate (0.80 g) in tetrahydrofuran (10 ml) under nitrogen atmosphere at 0 °C. The temperature was returned to room temperature and the mixture was stirred for 1 hour. Then, to the mixture was added dropwise a solution of 3-methoxybenzyl bromide (2.29 g) in tetrahydrofuran (5 ml) at 0 °C. The temperature was returned to room temperature, and the mixture was stirred for 3 days. To the mixture were added ethyl acetate and water, and the mixture was separated. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure and the resulting residue was purified with silica gel column chromatography (hexane: ethyl acetate = 5:1) to give methyl 7-bromo-1-(3-methoxybenzyl)-2,3-dihydro-1-benzazepine-4-carboxylate (0.69 g) as yellow oil.

Please insert the following paragraph as the first paragraph on page 393 of the specification.

✓ Page 393, paragraph 1 (AMENDED) ✓

B48

water at 0 °C, and 1N hydrochloric acid was further added to neutralize, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, which was recrystallized from hexane-ethyl acetate to give 7-(4-butoxyethoxyphenyl)-1-[(1-methylpyrazol-4-yl)methyl]-2,3-dihydro-1-benzazepine-4-carboxylic acid (239 mg) as yellow crystals.

Please insert the following paragraph as the second paragraph on page 412 of the specification.

✓ Page 412, paragraph 2 (AMENDED) ✓

B49

Reference Example 223

To a solution of methyl 7-bromo-2,3-dihydro-1-benzazepine-4-carboxylate (200 mg) and pyridine (123 mg) in tetrahydrofuran (10 ml) was added 2-thienyl chloride (208 mg) at 0 °C, and the mixture was heated at 78 °C overnight. After allowing to cool, to the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with magnesium sulfate. The solvent was evaporated, which was recrystallized from hexane-ethyl acetate to give methyl 7-bromo-1-(2-thienylcarbonyl)-2,3-dihydro-1-benzazepine-4-carboxylate (236 mg) as colorless crystals.

Please insert the following paragraph as the second paragraph on page 424 of the specification.

✓ Page 424, paragraph 2 (AMENDED) ✓

B50

Reference Example 236

In toluene (100 ml), ethanol (10 ml) and water (10 ml) were suspended methyl 7-bromo-2,3-dihydro-1-benzazepine-4-carboxylate (3.0 g), 4-propoxyethoxyphenyl borate (3.1 g) and potassium carbonate (3.8 g), and the suspension was stirred for 30 minutes under argon atmosphere. Then, to the suspension was added tetrakis(triphenylphosphine)palladium (860 mg), and the mixture was heated at 100 °C for 8 hours under argon atmosphere. After allowing to cool, water was added thereto, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane: ethyl acetate = 3: 1) to give the solid, which was washed with hexane

contd.

B50

to give methyl 7-(4-propoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylate (2.59 g) as yellow crystals.

Please insert the following paragraph as the second paragraph on page 425 of the specification.

✓ Page 425, paragraph 2 (AMENDED) ✓

B51

Reference Example 237

In toluene (200 ml) and ethanol (35 ml) were suspended methyl 7-bromo-2,3-dihydro-1-benzazepine-4-carboxylate (5.0 g), 4-butoxyethoxyphenyl borate (4.6 g) and 1M potassium carbonate solution (35 ml), and the mixture was stirred for 30 minutes under argon atmosphere. Then, to the mixture was added tetrakis(triphenylphosphine)palladium (1 g), and the mixture was heated at 100 °C overnight under argon atmosphere. After allowing to cool, to the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane: ethyl acetate = 4:1) to give the solid, which was washed with hexane to give methyl 7-(4-butoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylate (5.7 g) as yellow crystals.

TO2121-1228FOOT

Please insert the following paragraph as the second paragraph on page 430 of the specification.

✓ Page 430, paragraph 2 (AMENDED) ✓

B52

Reference Example 243

In toluene (15 ml), ethanol (1.5 ml) and water (1.5 ml) were suspended methyl 7-bromo-[(1-ethylpyrazol-4-yl)methyl]-2,3-dihydro-1-benzazepine-4-carboxylate (550 mg), 4-propoxyethoxyphenyl borate (320 mg) and potassium carbonate (506 mg), and the suspension

contd.
B52

was stirred for 30 minutes under argon atmosphere. Then, to the suspension was added tetrakis(triphenylphosphine)palladium (81 mg), and the mixture was heated at 100 °C for 6 hours under argon atmosphere. After allowing to cool, water was added thereto, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane: ethyl acetate = 1:1) to give methyl 1-[(1-ethylpyrazol-4-yl)methyl]-7-(4-propoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylate (370 mg) as yellow oil.

Please insert the following paragraph as the first paragraph on page 432 of the specification.

✓ Page 432, paragraph 1 (AMENDED) ✓

B53

In methanol (25 ml) and THF (10 ml) was dissolved methyl 7-[(4-(2-butoxyethoxy)phenyl)-1-(2-methylthiazol-4-yl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.17 g). To the solution was added 1N sodium hydroxide solution (4 ml), and the mixture was stirred at room temperature overnight, heated at 60 °C for 5 hours, concentrated, neutralized with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated to give 7-[4-(2-butoxyethoxy)phenyl]-1-(2-methylthiazol-4-yl)-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.12 g) as yellow crystals.

Please insert the following paragraph as the second paragraph on page 436 of the specification.

✓ Page 436, paragraph 2 (AMENDED) ✓

Reference Example 249

B54 In toluene/ethanol/water (=10/1/1, 41 ml) was dissolved methyl 7-bromo-1-isobutyl-2,3-dihydro-1-benzazepine-4-carboxylate (0.90 g). To the solution were added 4-(2-propoxyethoxy)phenyl borate (0.72 g) and potassium carbonate (0.81 g) and the mixture was stirred for 30 minutes under argon atmosphere. To the mixture was added tetrakis(triphenylphosphine)palladium (123 mg) and the mixture was heated to reflux for 14 hours. After cooling to room temperature, the solution was added to water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried with magnesium sulfate. The solvent was removed under

Please insert the following paragraph as the first paragraph on page 494 of the specification.

✓ Page 494, paragraph 1 (AMENDED) ✓

B55 room temperature, and the solvent was removed under reduced pressure. The resulting residue was added to water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (ethyl acetate/ethanol = 15: 1) to give methyl 7-[4-(2-butoxyethoxy)phenyl]1-(tetrazol-5-ylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylate (0.67 g).

Please insert the following paragraph as the second paragraph on page 523 of the specification.

Page 523, paragraph 2 (AMENDED)

B56

Reference Example 306

To a solution of methyl 7-[4-(2-butoxyethoxy)phenyl]-1-[(2-methyl-1,3-dioxolan-2-yl)methyl]-7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (795.7 mg) in a mixture of THF-methanol (5-5 ml) was added 1N sodium hydroxide solution

Please insert the following paragraph as the second paragraph on page 529 of the specification.

Page 529, paragraph 2 (AMENDED)

B57

Reference Example 311

4-morpholinophenyl borate (237 mg) and 7-bromo-1-propyl-N-[4-[[N-methyl-N-(tetrahydropyran-4-